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Inflammatory Response of Skeletal Muscles to a High-Fat Diet

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SUMMARY

Background. The prolonged consumption of a high-fat diet (HFD) leads to abnormal growth of the adipose tissue, development of obesity and low-grade inflammation. However, the data about dietary-induced inflammation in muscles is scarce. Therefore, we estimated the inflammatory response to a HFD of different skeletal muscles in a rat model.
Materials and methods. Eight-week-old male Wistar rats were subjected to a high-fat (n = 36) or standard diet (n = 24). After fourteen weeks, tissue samples were collected from twelve animals from each group. To assess the effect of diet duration, twelve of the remaining animals from the experimental group were then subjected to a standard diet, while all the other animals continued with their previous diet for four more weeks. The levels of the pro-inflammatory markers CRP and serum amyloid-A (SAA) and the anti-inflammatory IL-4 were determined by ELISA in tissue homogenates from gastrocnemius, soleus and extensor digitorum longus (EDL) muscles.
Results. In general, the HFD elevated slightly muscle levels of the acute phase proteins and its longer duration led to an additional increase, but the increment followed different pattern, time-dependence and statistical significance in the different skeletal muscles. The gastrocnemius muscle was the most, while the EDL the least responsive. The effect of HFD was more pronounced and faster on CRP than SAA levels. The replacement of the HFD with a standard diet led to restoration of the normal, non-inflammatory phenotype of the muscles, whereas IL-4 levels were almost unchanged during the experiment.
Conclusions. The HFD results in low-grade, chronic inflammation in skeletal muscles which is time-dependent and muscle-specific, but the muscle tissue is less likely to exert control over the development of this process.
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KEY WORDS

High-fat diet; skeletal muscles; low-grade inflammation; serum amyloid-A; CRP; interleukin-4; animal model.

BACKGROUND

Inflammation is a normal component of the human self-defense mechanisms (1). It is both a cellular and a specific organismal response to various stressful situations such as viral infections, tissue damage or other tissue stress factors. Regardless the reason that provokes it, it is considered to be a process that aids the restoration of the functional and phenotypic homeostasis of the damaged cell, tissue or organ (2).

There is a plenty of data about the effects of obesity on the inflammatory process. The prolonged consumption of a

high-fat diet (HFD) leads to abnormal growth of the adipose tissue and development of obesity. In turn, obesity has been associated with changes in the immune cells' composition in the tissue and development of low-grade, chronic inflammation (3). This type of inflammation differs from the acute inflammation since the levels of the circulating pro-inflammatory marker molecules are only slightly elevated (4, 5). It appears to be caused by many different factors such as excessive calories intake, changed food composition and unusual homeostasis (5).

Many authors have published that the liver also develops low-grade inflammation as a result of obesity and a changed number of macrophages in the organ (6-8). The unfavorable effects of lipids on muscles are described also in obesity-linked disorders such us insulin resistance and metabolic syndrome. It has been reported that they are characterized with hyperlipidemia and dyslipidemia, which in turn is associated with the formation of fat depots in muscles and tendons (9). These findings are supported and expanded to the increased infiltration of lipids into muscle cells (10) and their adverse effects on muscle tissue phenotype restoration and impaired healing processes (11).

At the same time clear and reliable information about the inflammatory response of skeletal muscles to a HFD in healthy individuals and its early dynamics is still insignificant. The aim of the present study was to evaluate the development of dietary-induced inflammation using an animal model, and measuring the levels of the pro-inflammatory, acute-phase proteins – C reactive protein (CRP) – and serum amyloid-A (SAA) –, and the anti-inflammatory interleukin-4 (IL-4).

METHODS

This study has an approval for the usage of laboratory animals in experiments from the Bulgarian Agency for Food Safety (BAFS – resolution n. 55/23.06.2016), and it is in accordance with the ethical standards of the Medical University of Plovdiv (resolution of the University Ethics Committee – n. P-1041/25.04.2017 – Date of approval: April 25, 2017).

Sixty, 8-week-old male Wistar rats (weight 130-180 g) were used for the needs of this experiment. They were randomly divided into two groups:

1. Control group (C, n = 24), fed with standard rodent food (D12450H, Research Diets, Inc.) for 14 weeks.
2. Experimental group (E, n = 36), fed with a HFD (D12451 – Research Diets, Inc.) for 14 weeks.

All animals were maintained under standard housing conditions, they were all fed *ad libitum* and were housed at 12 h light/dark cycles (12). Twelve animals were taken at random from each group after 14 weeks and tissue samples were collected and stored (12). The tissue samples obtained were from three different skeletal muscles: musculus gastrocnemius (m. Gas), musculus soleus (m. Sol) and musculus extensor digitorum longus (m. EDL). The decision to collect these muscles was based on the specific distribution of muscle fibers with characteristic physiology and metabolism: m. Sol consists of 85% type I muscle fibers, m. EDL of 96% type II muscle fibers and m. Gas of 51% type I and 49% type II muscle fibers (13).

The remaining animals were divided into new groups as following:

1. the animals from the control group were established into a new control group (CC, n = 12). They all continued to be fed with standard food (D12450H, Research Diets, Inc.) for four more weeks.
2. The experimental (E) group was split into two new groups:
   - 2.1. Experimental group (EE, n = 12) – fed the same HFD for four more weeks
   - 2.2. Experimental group (EC, n = 12) – the diet of the animals from this group was changed from the high-fat to the standard diet. They were all fed with the standard food for the next four weeks.

The duration period of the experiment was eighteen weeks in total for the animals from the three new groups. The same procedure was followed when the tissue samples were collected at the end of our experiment (12).

The quantitative ELISA method was used to determine the concentration of CRP, SAA and IL-4 in the tissue homogenates, while the Lawry method (14) was used for the determination of the total protein concentration of the same samples. The levels of CRP, SAA and IL-4 in the studied tissues are present as a ratio of the concentration of the marker in the sample to the total protein concentration in the same tissue sample (ng CRP/mg Protein, ng SAA/mg Protein and pg IL-4/mg Protein).

The collected data was statistically processed by SPSS, v.19.0 (SPSS Inc., Chicago, IL, USA). The results were compared by Kruskal-Wallis test for non-parametric data and are present as median (25^{th}-75^{th} percentile). Differences with P-values less than 0.05 were considered as statistically significant. The Dunn's *post-hoc* test was performed for those groups where statistical difference was found.

RESULTS

Development of inflammation in m. Gas

The levels of both pro-inflammatory marker molecules CRP and SAA, measured in samples from m. Gas, showed

statistically significant differences among the experimental groups. The levels of CRP, measured in the experiment group "E" – 15.07 ng/mg (8.39-20.19 ng/mg) – were significantly higher than the CRP levels in the control group "C" – 5.61 ng/mg (4.02-7.84 ng/mg), $p < 0.05$. This diference was even more pronounced when the experiment group "EE" – 26.93 ng/mg (17.6-38.77 ng/mg) was compared with either of the control groups "C", $p < 0.01$, or "CC" – 5.32 ng/mg (2.91-6.99 ng/mg), $p < 0.01$. Differences were detected even between groups "E" and "EE", $p < 0.05$. The detected values for CRP in the group "EC" – 15.04 ng/mg (11.61-20.62 ng/mg) were still high. They were close to those detected for groups "E" and "EE", $p > 0.05$ and much higher than those observed in the control groups, $p < 0.05$ (**figure 1 A**).

The changes in the levels of SAA followed a similar patern as the changes for CRP. The levels were high and there was a statistically significant difference detected on week 14. The levels in the control group "C" – 26.12 ng/mg (22.61-38.64 ng/mg) were much lower than in the experimental group "E" – 64.58 ng/mg (39.18-88.76), $p < 0.01$. In contrast to the changes in the levels of CRP, the SAA levels did not show any dependence on time. The levels of SAA in the experimental group "EE" – 45.75 ng/mg (35.39-70.78 ng/mg) – were almost the same as its quantity in the group "E", $p > 0.05$, but significanly higher than in both control groups "C" and "CC" – 24.71 ng/mg (22.61-31.39 ng/mg), $p < 0.05$. The quantitative analysis of SAA in the group where the diet was changed from high-fat to standard showed that the marker levels are of intermediate values. They were close to the values of the control groups "C" and "CC" on one side, $p > 0.05$, but comparatively lower than those of the experiment groups "E" and "EE", $p < 0.05$, on the other (**figure 1 B**).

The levels of the anti-inflammatory IL-4 molecule were very close and with no significant differences among the groups: "C" – 7.74 pg/mg (3.74-15.32 ng/mg), "CC" – 5.62 pg/mg (4.29-7.55 ng/mg), "E" – 11.73 pg/mg (9.19-14.7 ng/mg), "EE" – 9.97 pg/mg (7.35-17.47 ng/mg), "EC" 9.52 pg/mg (4.19-12.24 ng/mg), $p > 0.05$ (**figure 1 C**).

Development of dietary-induced inflammation in m. Sol

We established that m. Sol responds to the HFD with changes in the levels of both pro-inflammatory markers, $p < 0.01$. The levels of CRP were high in both groups fed only with the HFD. The quantity of CRP in the group "E" – 13.82 ng/mg (7.2-14.57 ng/mg) and "EE" – 13.1 ng/mg (11.61-16 ng/mg) was significantly higher when compared with the control group "C" – 6.04 ng/mg (3.21-9.44 ng/mg), $p < 0.05$. The CRP levels measured in the second control group "CC" – 8.34 ng/mg (7.34-9.55 ng/mg) and the "EC" group – 11.27 ng/mg (6-14.79 ng/mg) were similar to those of the control group "C", $p > 0.05$, and the groups "E" and "EE", $p > 0.05$ (**figure 2 A**).

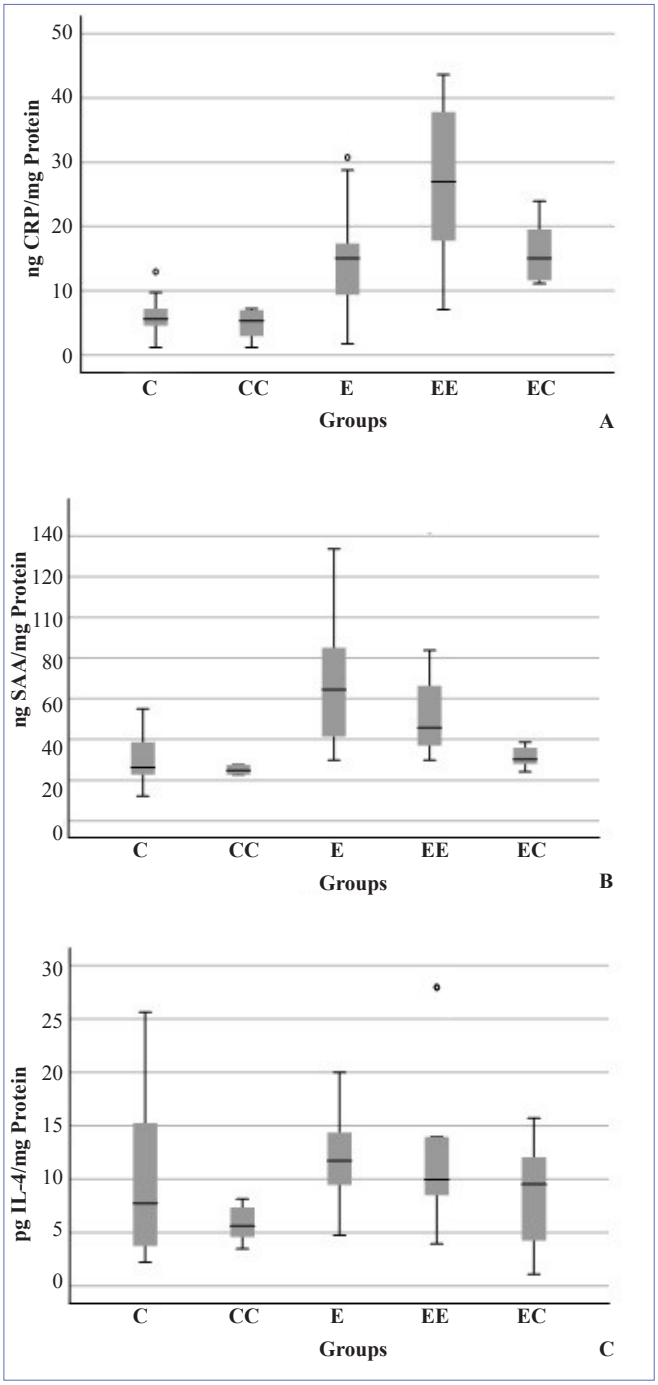

Figure 1. Changes in the levels of CRP, SAA and IL-4 in tissue homogenates, obtained from m. Gas.

The quantitative analysis of SAA in samples from m. Sol showed no significant differences between the control groups "C" – 25.63 ng/mg (20.31-33.19 ng/mg), and "CC" – 27.27 ng/mg (17.39-47.6 ng/mg) with the experiment group "E" – 27.02 ng/mg (19.48-30.02), p > 0.05.

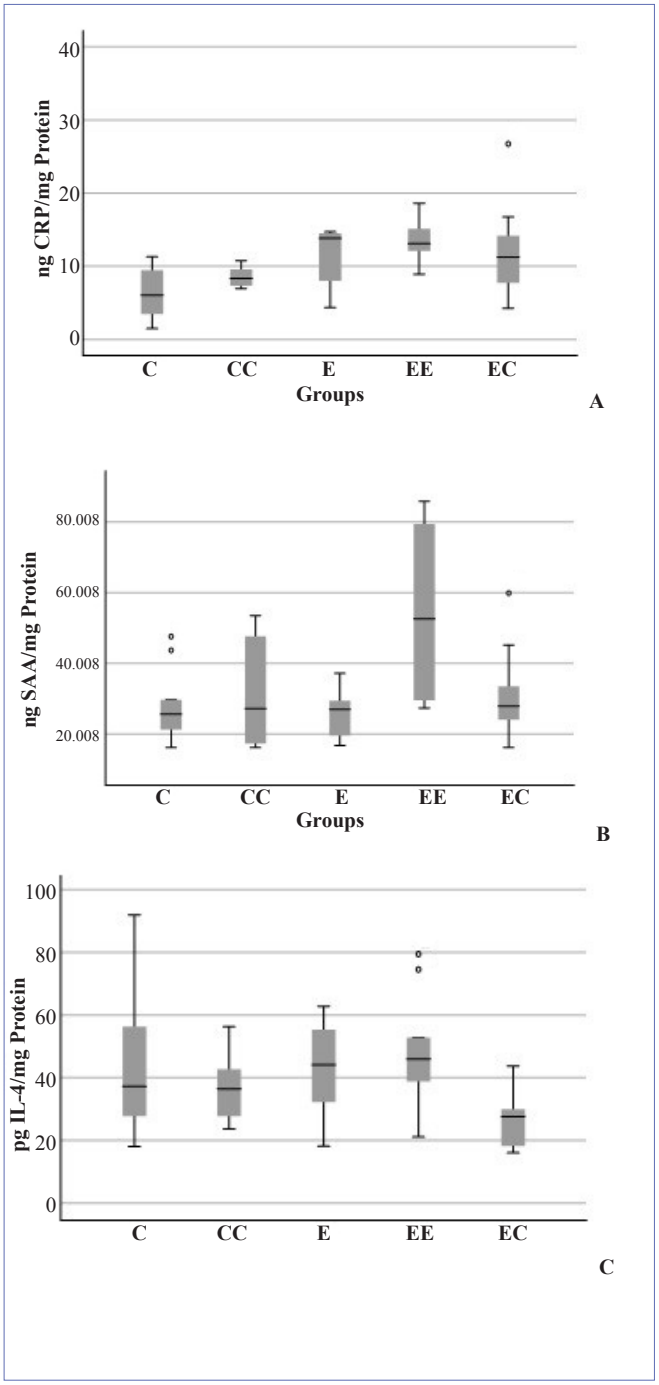

Figure 2. Changes in the levels of CRP, SAA and IL-4 in tissue homogenates obtained from m. Sol.

However, the prolonged consumption of the lipid-rich food caused changes in the levels of the proi-nflammatory marker – the levels were significantly higher in the group "EE" – 52.54 ng/mg (29.46-79.5 ng/mg). The quantity of SAA in this group was much higher than in all other groups, p < 0.05. We also detected that when the animals stopped taking the high-lipid food and returned to the standard diet, the values of the marker – group "EC" – 27.93 ng/mg (22.44-36.4 ng/mg) were also decreased and close to their normal, control group values, p > 0.05 (**figure 2 B**).

The quantitative analysis of the IL-4 levels in m. Sol demonstrated a lack of statistically significant differences amongst the compared groups: "C" – 37.18 pg/mg (26.75-64.15), "CC" – 36.45 pg/mg (26.75-46.12), "E" – 44.12 pg/mg (28.72-56.98), "EE" – 45.94 pg/mg (35.35-58.23) and "EC" – 27.55 pg/mg (17.59-33.41), p > 0.05 (**figure 2 C**).

Dietary-induced changes in m. EDL

Development of inflammation was detected in m. EDL, similarly to the previously described muscles. Using the Kruskal-Wallis test, we established an increase in the levels of CRP only p < 0.01. The comparison between the values in the group "C" – 9.1 ng/mg (2.4-11.58 ng/mg) on one hand, and the groups "E" – 15.76 ng/mg (9.83-24.9 ng/mg) and "EE" – 13.76 ng/mg (12.82-28.14 ng/mg), p < 0.05, on the other, gave evidance for us to state that there is an inflammatory process. Similar dependence was observed when both the "E" and "EE" groups were compared to the control group "CC" – 6.39 ng/mg (3.01-7.77 ng/mg), p < 0.01. Decreased CRP levels as a result of suspended high-lipid intake were detected in this muscle only. The CRP values in the "EC" – 9.6 ng/mg (7.5-12.16 ng/mg) are much lower than those in the experimental groups, p < 0.05 and very close to the levels in the control groups, p > 0.05 (**figure 3 A**).

The comparison of the levels of SAA in tissue homogenates from m. EDL: "C" – 12.73 ng/mg (10.1-16.85 ng/mg), "CC" – 13.28 ng/mg (12.61-14.95 ng/mg), "E" – 16.81 ng/mg (13.83-18.74 ng/mg), "EE" – 22.7711 ng/mg (12.47-30.4 ng/mg) and "EC" – 14.52 ng/mg (13.28-17.2 ng/mg), did not show any significant differences, p > 0.05 (**figure 3 B**).

It was interesting to find that the changes in the quantity of IL-4 did not follow the pattern, detected in the previously described muscles. The quantity of IL-4 was significantly higher in the "EE" group – 21.81 pg/mg (14.41-24.73 ng/mg), than in the control groups "C" – 6.61 pg/mg (4.37-11.65 ng/mg) and "CC" – 4.84 pg/mg (4.04-6.05 ng/mg), p < 0.01. At the same time the amount of IL-4 established in the group "EC" – 4.01 pg/mg (3.53-14.17 ng/mg) was almost the same as the amount of the marker in the groups "C" and "CC", p > 0.05 (**figure 3 C**).

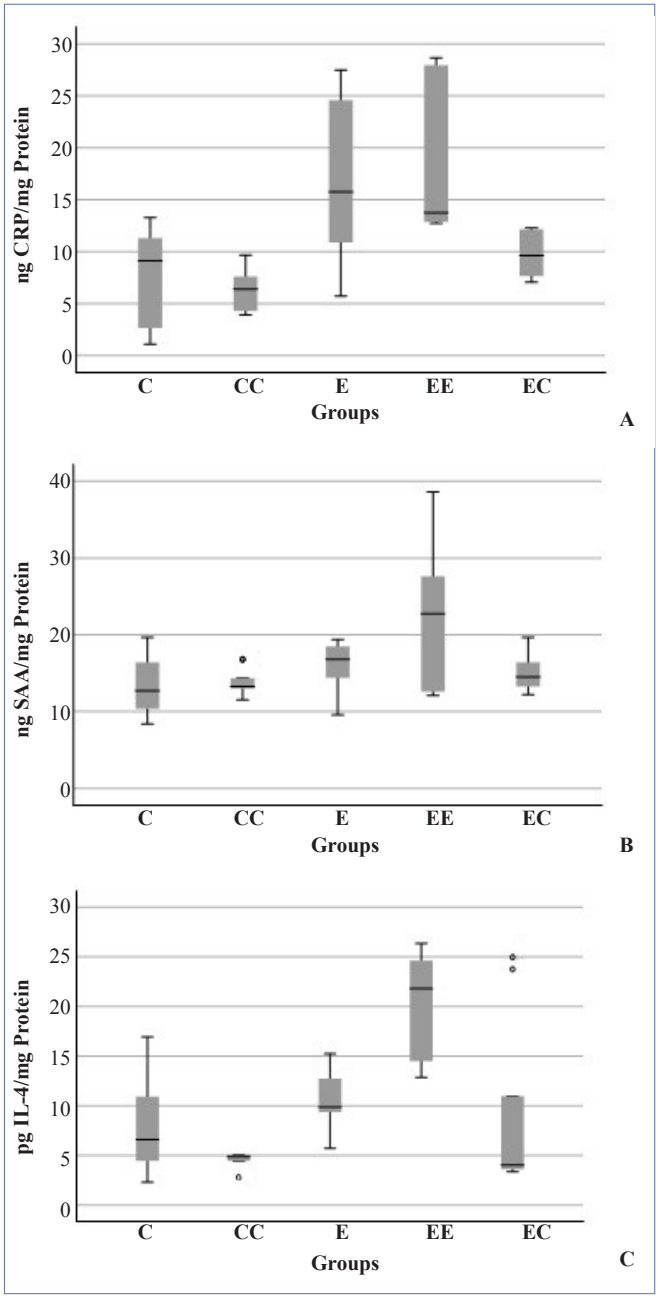

Figure 3. Changes in the levels of CRP, SAA and IL-4 in tissue homogenates obtained from m. EDL.

DISCUSSION

The process of tissue inflammation requires well-coordinated cytokine secretion, as well as activation and infiltration of immune cells in the tissues (15). In summary, our experiment established increased levels of both pro-inflammatory marker molecules in the tested tissues. The elevation of their levels followed a different pattern and depended on time in a different way for each of the markers. At the same time, the changes in the levels of the anti-inflammatory molecule followed neither the same pattern, nor similar dependence on time. All the above mentioned could be a result of an impaired intercellular communication, as well as disturbance in the normal differentiation of the cells and/or normal tissue remodeling (16).

Many studies have demonstrated that both pro- and anti-inflammatory molecules are present in the food (17, 18). It has been reported that saturated fatty acids can influence the development of an inflammatory process, affecting intracellular signaling pathways that use nuclear factor kappa-B and the family of peroxisome proliferator-activated receptors (19). The pro-inflammatory effects are triggered by a family of receptors called toll-like receptors (TLR), that are found on the plasma membrane of the immune system cells and on muscle cells (20). It has also been reported that the number of these receptors on the muscle cells varies and depends on the diet (21). It has been proposed that the muscle tissue develops inflammation in obesity. This type of inflammation depends on the increased infiltration of immune cells on one hand, and the pro-inflammatory phenotype of the adipose tissue located in the skeletal muscles, on the other. The inflammatory process and muscle metabolism could be also affected by an increased influx of free fatty acids (FFA) and/or pro-inflammatory molecules, secreted by many other cells and tissues, including the visceral adipose tissue (22).

Another possible reason for the development of an inflammatory process could be the tissue composition. Tissue macrophages are constantly present in the skeletal muscles, as well as in other tissues like the adipose tissue and liver. They are responsible for the tissue damage repair (23). Additional infiltration of a tissue by activated macrophages could be due to an increased concentration of FFA, tissue damages or adipose tissue depots in skeletal muscles (24, 25). Tissue macrophages could be also transformed into activated macrophages that exhibit proiflammatory phenotype. All the above mentioned supports our findings that the prolonged consumption of a HFD could provoke the development of inflammation in the skeletal muscles (26).

Our experiment detected that the levels of CRP increase faster than the levels of SAA or that there is a complete lack of changes in the levels of SAA. The changes in the CRP levels were dependent on time only in m. Gas. This could be explained with the assumption that the HFD could affect the amount of the pro-inflammatory molecules at many levels. Firstly, the increased levels of FFA, are associated with an increased infiltration of macrophages into the muscles. These macrophages are found mainly in intramuscular fat depots, which increase in number and volume in obesity (27). It has been proposed that pro-inflammatory molecules could be

released from such depots to provoke paracrine effects on the development of inflammation in the neighboring muscle cells (28, 29). Secondly, it has been reported that muscle infiltrated macrophages secrete pro-inflammatory cytokines such as IL-6 when placed in a medium with excess of FFA (30). Thirdly, *in vitro* studies with m. Sol placed in a FFA-rich medium, have demonstrated the release of pro-inflammatory molecules such as IL-6 and TNF-α from the muscle cells (26, 31). All these observations propose the existence of many and complex interrelationships between the cells to respond to the intake of the HFD (26). All the reasons listed above might be responsible for the different timing of the inflammatory process as well as for modulation of its development. The receptors that belong to the group of the TLRs are among the most important participants in the development of inflammation and exhibition of the effects of an HFD. It has been reported that the expression of TLR2 and TLR4 is higher in skeletal muscles subjected to a HFD (21). Overexpression of the receptor, higher body weight, decreased glucose and insulin tolerance were reported for rodents consuming such a diet (32).

Skeletal muscles differ in the degree of blood supply and the amount of mitochondria, hence the intake of a HFD leads to an increased degree of oxidation of fatty acids in the mentioned muscles. This process requires a relatively short period of HFD intake (about eight weeks) to be detected. Nevertheless, there is no evidence of additional activation of antioxidant enzymes, which would lead to the manifestation of the negative effects of reactive oxygen species (33). Furthermore, the distribution of different isoforms of myosin fibrils and the ratio between them is another factor that changes the metabolism of fast and slow-twitch muscles. The lipid origin and composition of the diet have also been shown to change the muscle phenotype (34). The slightly elevated levels of CRP and SAA are indicative for the development of low-grade inflammation. One of the main reasons for the elevated levels of SAA in obesity is the increased infiltration rate of macrophages into the adipose tissue, where it aids the removal of cholesterol, released from the damaged tissue (35). We observed that the changes in the levels of SAA followed the same pattern as the CRP levels, but only in m. Gas. In m. Sol the levels of SAA increased significantly only as a result of the longer intake of the HFD. Therefore, we could assume that m. Gas is more responsive to the high-fat diet than m. Sol and especially m. EDL.

Studies with human patients with obesity and diabetes mellitus type II have demonstrated increased levels of macrophages and T-cells in the skeletal muscles. Increased macrophage levels have also been observed in the skeletal muscles of healthy patients as a result of the intake of a HFD even for a short period of time (36). Extrapulating our results from an animal model to humans, we could speculate that the prolonged consumption of a Western type of diet, rich in fats, might induce chronic, low-grade inflammation long before clinical manifestations of insulin resistance and furhter metabolic disturbances.

All the reasons mentioned above link the consumption of a HFD with the development of inflammation in the skeletal muscles. The inflammatory process is characterized with increased levels of pro-inflammatory molecules which in turn mediate the development of inflammation in the muscle tissue (21).

CONCLUSIONS

Skeletal muscles constantly respond to the changes in their surrounding environment. The increased levels of the pro-inflammatory molecules observed in our *in vivo* experiment, support the hypothesis that skeletal muscles develop inflammation as a result of the intake of a high-fat diet. This inflammation affects all the muscles tested during the experiment. The tendency for a decrease in the levels of the pro-inflammatory markers after the high-fat diet cessation suggests that the dietary-induced inflammation is a reversible process. The insignificantly changed levels of the anti-inflammatory molecule indicate that the muscle tissue does not, or barely exerts control over the development of the inflammatory process. Our data might be useful for epigenitic studies elucidating the impact of diet in heathly individuals in the very early stages of development of mucsle low-grade inflammation which can be the triggering factor of later insulin resistance.

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DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

The main idea and the initial organization belonged to associate professor Vassil Kamenov, MD who unfortunately passed away in the early 2021. All authors: writing, methodology, data analysis.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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